Applying Chimeric Antigen Receptor T cells (CAR-T) to hematologic malignancies

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How are CAR-Ts made?

1. Extracting T cells: A patient is hooked up to a machine that separates out white blood cells, including T cells, and returns red cells and platelets to the patient. The resulting bag of cells is sent to the manufacturing facility for reprogramming.

2. Reprogramming: At the manufacturing facility, a viral vector inserts into T cells the genes carrying the instructions for a chimeric antigen receptor, or CAR. The CAR consists of an antibody domain that can recognize specific cancer cells; a hinge and transmembrane domain that attaches the antibody to the cell; and costimulatory and essential activity domains, which together signal the cell to divide.

3. Manufacturing: To elicit a powerful response in the patient, oncologists need to return many more of the reprogrammed T cells than they draw out. Reprogrammed T cells are "expanded" in a bioreactor with the help of magnetic beads coated with two antibodies, anti-CD3 and anti-CD28, that signal the T cells to proliferate. After the expansion, which takes about 10 days, the magnetic beads are washed out.

4. Patient preparation: The patient is given chemotherapy to lower his or her white blood cell count, thus increasing the chance that the immune system will accept the modified T cells.

5. Treatment: The reprogrammed T cells are infused back into the patient's blood. Once in circulation, they search for and destroy cancer cells expressing the antigen targeted by the CAR.

http://cen.acs.org/articles/92/i40/Immune-System-Fights-Back.html
Accessed 3/14/2016
Cytotoxicity of CD19-specific CAR-expressing T Lymphocytes against B Cell Lymphoma

Amended Courtesy of Keiya Ozawa, Professor, Div. Genetic Therapeutics at the University of Tokyo
From the 6th International Hematologic Malignancies Conference
What is all the buzz about?

- Remissions occurring in high risk, multiple relapsed disease
- Toxicities can be severe but they are transient
Clinical Results

• Relapsed/refractory ALL
  – Adults 5 year OS <10% with chemotherapy
  – Pediatric 5 year OS 27% with chemotherapy
  – Novel therapies such as blinatumumab in multiply relapsed ALL: Median OS 7.7 months

• CAR-T therapy
  – 90% Complete remission rate

Maude et al. NEJM 2014;371:1507017
Durable Remissions

6 month EFS 67%

6 month OS 78%

Maude et al. NEJM 2014;371:1507017.
Notable Adverse Events

- Cytokine Release Syndrome
- Neurologic
- B Cell Aplasia
- Off target effects
- Expense
Cytokine Release Syndrome

Orlowski RJ et al. BJH epub 2016.
Figure 1. CRS toxicities by organ system. After infusion of CAR T cells, CRS toxicities affecting a wide variety of organs can occur. Professional illustration by Patrick Lane, SciEYEnce Studios.
Clinical Appearance of CRS

- Differential diagnosis of signs/symptoms is broad
- Timing hours to over a week after CarT infusion

- **Fever:** Frequently 1st sign; often >40 C
  - Grade 3-4 reported in 40-80% of patients
- **CV:** tachycardia, hypotension, arrhythmias, decreased left ventricular ejection fraction
  - Grade 3-4 hypotension in 22-38% of patients
- **Pulmonary:** edema, hypoxia, intubations, pneumonitis
  - Grade 3-4 hypoxia 6-15% of patients
- **Acute renal failure, transaminitis, cytopenias, derangements of coagulation**

Cytokine Release Syndrome

- Grade 1: Fever, constitutional symptoms

- Grade 2:
  - Hypotension responsive to fluids or 1 low dose pressor
  - Hypoxia requiring <40% FiO2
  - Organ toxicity: grade 2

- Grade 3:
  - Hypotension requiring multiple pressors
  - Hypoxia requiring ≥ 40% FiO2
  - Organ toxicity grade 3 any organ or grade 4 transaminitis

- Grade 4:
  - Mechanical ventilation
  - Organ toxicity grade 4 (excluding transaminitis)

100% had Cytokine Release Syndrome

• Mild to moderate CRS 22/30 (73%)
  – Started a median of 4 days after infusion
  – Hospitalized for febrile neutropenia and IV Abx

• Severe 8/30 (27%)
  – Defined as hypotension requiring 2 or more vasopressors or respiratory failure requiring mechanical ventilation
  – Started a median of 1 day after infusion
• 30 patients with rel/ref B cell NHL
  – 16 patients had CRS
    • Grade 2 in 14
    • Grade $\frac{3}{4}$ in 2

CRS Management Algorithm

**Grade 1 CRS**
Fever, constitutional symptoms

**Grade 2 CRS**
Hypotension: responds to fluids or one low dose pressor
Hypoxia: responds to <40% O₂
Organ toxicity: grade 2

**Grade 3 CRS**
Hypotension: requires multiple pressors or high dose pressors
Hypoxia: requires ≥ 40% O₂
Organ toxicity: grade 3, grade 4 transaminitis

**Grade 4 CRS**
Mechanical ventilation
Organ toxicity: grade 4, excluding transaminitis

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**TREATMENT**

- Vigilant supportive care
- Assess for infection
  (Treat fever and neutropenia if present, monitor fluid balance, antipyretics, analgesics as needed)

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- Vigilant supportive care
  (Monitor cardiac and other organ function closely)

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- Vigilant supportive care
  - Tocilizumab
  ± corticosteroids

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Tocilizumab: Anti-IL6

A Low IL-6 Levels: Classic IL-6 Signaling

B High IL-6 Levels: Classic- and Trans-Signaling Inhibited by Tocilizumab

Tocilizumab failures

- Second dose of tocilizumab
- Steroids
  - Not given 1st line
  - May inhibit CAR T cell persistence
- Some other agents tried: infliximab, etanercept
Management of Severe CRS

- Tocilizumab –
  - 5 patients x 1 dose and 4 patients x 2 doses
  - Rapid defervescence
  - Stabilization of BP with vasopressors weaned over 1-3 days

- Course of steroids in 6 patients
- All patients recovered completely

- 2/9 patients had a relapse of their ALL

Maude et al. NEJM 2014;371:1507017.
Neurologic Toxicity

• Delirium, encephalopathy, aphasia, confusion, hallucinations, seizure, cranial nerve palsy

• Secondary to CRS?
  – High dose Interleukin-2 therapy
  – Blinatumumab
  – Neuro toxicity sometimes occurs w/o CRS

• Secondary to a direct anti CD-19 effect in CNS?
  – Blinatumumab
  – Anti-CD19 CarT cells found in CSF

Neurologic Toxicity

• Acute lymphoblastic lymphoma patients

• 13/30 (43%) had neurologic toxicity
  – 6 patients it was delayed occurring after fevers and CRS had resolved
  – When performed, head MRI/CT were negative and LPs negative for infection/leukemia

• Spontaneous complete resolution over 2-3 days

Maude et al. NEJM 2014;371:1507017.
Management Neuro Toxicity

- Close monitoring for symptoms
  - Routine neurologic exams
  - Routine mini mental status exam testing

- Management
  - Brain MRI
  - Lumbar puncture
  - Neurology consult
  - Anti-epileptics if seizures occur

Dexamethasone

Grade 3 neurologic toxicities, with the exception of headaches, that last continuously for 24 h or longer;
Grade 4 neurologic toxicity of any duration; and
Any generalized seizure

10 mg IV q 6 h until either:
Toxicities improved to grade 1 or less, or
At least 8 doses have been given

These are the current treatment guidelines used for adult patients at the NCI Experimental Transplantation and Immunology Branch.

B Cell Aplasia

- Hypogammaglobulinemia
- Occurs in up to 100% of responders
- Persisted for up to a year after CTL019 cells undetectable by flow cytometry
- Pharmacodynamic measure of CTL019 function

- Most patients receive IVIG if IgG < 400 or 500mg/dL
  - Hypogammaglobulinemia in CLL
    - IVIG if IgG < 500mg/dl
      - And
    - Recurrent severe sinopulmonary infections

- Need to re-vaccinate?

Maude et al. NEJM 2014;371:1507017.
Off target effects

- CarT cells could damage normal tissue expressing the targeted antigens
- Exhaustive search for antigen on normal tissue is done during CarT development
- Metastatic Renal Cell Cancer
  - CarT targeting carboxy-anhydrase-IX
  - Grade 3-4 increases in AST/ALT/T Bili
  - Liver biopsy:
    - Cholangitis
    - T cell infiltrate around bile ducts
    - Bile duct epithelial cells found to express carboxy-anhydrase-IX

In Girl’s Last Hope, Altered Immune Cells Beat Leukemia

By DENISE GRADY  DEC. 5, 2012

HEALTH | In Girl’s Last Hope, Altered Immune Cells Beat Leukemia

On a small number of patients, such home tailor drugs can be approved more quickly and efficiently, he said, with smaller studies than are needed for drugs with less obvious benefits.

“The economic model is totally acceptable,” Mr. Hoppenot said.

But such drugs tend to be extremely expensive. A prime example is the Novartis drug Gleevec, which won rapid approval in 2001 for use against certain types of leukemia and gastrointestinal tumors. It can cost more than $5,000 a month, depending on the dosage.

Dr. June said that producing engineered T-cells costs about $20,000 per patient — far less than the cost of a bone-marrow transplant. Scaling up the procedure should make it even less expensive, he said, but he added, “Our costs do not include any profit margin, facility depreciation costs or other clinical care costs, and other research costs.”
New Costly Cancer Treatments Face Hurdles Getting to Patients

Novartis, Juno Conduct New Studies on Leukemia Therapies

Dr. Brenner signed a deal in March to commercialize his own CAR research with Celgene.

Novartis and Juno say it is too early to speculate on price, although Dr. Usman agrees the challenge is getting the manufacturing process to “a viable level where it’s both affordable and attractive.”

While most analysts think it is too early to estimate potential revenue or price, Citigroup believes CAR therapies could cost in excess of $500,000 per patient, which it notes is roughly in line with the cost of a stem cell transplant.

“This technology needs to be widely developed and accessible to patients,” says Dr. DeAngelo. “If the cost is going to be a hindrance, it’s going to be a really sad day.”
Questions?